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Allogeneic Stem Cell Transplantation in Multiple Myeloma Relapsed after Autograft: A Multicenter Retrospective Study Based on Donor Availability

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Allogeneic stem cell transplantation (allo-SCT) using reduced-intensity conditioning (RIC) is a feasible procedure in selected patients with relapsed multiple myeloma (MM), but its efficacy remains a matter of debate. The mortality and morbidity related to the procedure and the rather high relapse risk make the use of allo-SCT controversial. In addition, the availability of novel antimyeloma treatments, such as bortezomib and immunomodulatory agents, have made allo-SCT less appealing to clinicians. We investigated the role of RIC allo-SCT in patients with MM who relapsed after autologous stem cell transplantation and were then treated with a salvage therapy based on novel agents. This study was structured similarly to an intention-to-treat analysis and included only those patients who underwent HLA typing immediately after the relapse. Patients with a donor (donor group) and those without a suitable donor (no-donor group) were compared. A total of 169 consecutive patients were evaluated retrospectively in a multicenter study. Of these, 75 patients found a donor and 68 (91%) underwent RIC allo-SCT, including 24 from an HLA-identical sibling (35%) and 44 from an unrelated donor (65%). Seven patients with a donor did not undergo allo-SCT for progressive disease or concomitant severe comorbidities. The 2-year cumulative incidence of nonrelapse mortality was 22% in the donor group and 1% in the no-donor group ($P < .0001$). The 2-year progression-free survival (PFS) was 42% in the donor group and 18% in the no-donor group ($P < .0001$). The 2-year overall survival (OS) was 54% in the donor group and 53% in the no-donor group ($P = .329$). In multivariate analysis, lack of a donor was a significant unfavorable factor for PFS, but not for OS. Lack of chemosensitivity after salvage treatment and high-risk karyotype at diagnosis significantly shortened OS. In patients who underwent allo-SCT, the development of chronic graft-versus-host disease had a significant protective effect on OS. This study provides evidence for a significant PFS benefit of salvage treatment with novel drugs followed by RIC allo-SCT in patients with relapsed MM who have a suitable donor.

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KEY WORDS: Reduced-intensity regimens, Novel drugs, Donor versus no-donor analysis

INTRODUCTION

The spectrum of treatment options for patients with relapsed multiple myeloma (MM) has changed dramatically over the past 10 years. The introduction of thalidomide, its analog lenalidomide, and the proteasome inhibitor bortezomib have expanded the therapeutic arsenal of salvage treatments. A response rate of 30%-60% and a median response duration of 6-12 months has been achieved [1-4]. Moreover, an improvement in overall survival from the time of

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relapse has been observed in patients treated with novel agents compared with patients who were never exposed to these agents [5]. However, the majority of patients develop resistance over time and continue to suffer recurrent relapses; thus, long-term disease control or cure cannot be achieved.

Allogeneic stem cell transplantation (allo-SCT) is a potentially curative option because of a tumor-free graft and a postulated graft-versus-myeloma effect. Compared with the other treatment modalities for MM, allo-SCT induces the highest rate of clinical complete responses and molecular responses [6,7]. However, despite improvements in supportive care and patient selection, allo-SCT with myeloablative conditioning has a nonrelapse mortality (NRM) of 20%-44% due to organ toxicities, graft-versus-host disease (GVHD), and infections [8,9]. Reduced-intensity conditioning (RIC) transplantation regimens were introduced in the late 1990s to reduce the toxicity of the preparatory regimens and to maintain the immunologic effect of donor lymphoid cells (ie, graft-versus-tumor effect) [10]. Currently, the most consolidated results of RIC allo-SCT have been reported in patients with newly diagnosed MM with an HLA-identical sibling donor after tumor burden reduction with high-dose therapy followed by autologous stem cell transplantation (auto-SCT). A few randomized trials have compared this strategy with auto-SCT alone [11-14], and 2 of those studies suggested superior event-free survival and overall survival (OS) in patients who underwent allo-SCT [12,13]. The use of RIC allo-SCT in relapsed patients has been tested only in retrospective trials and in only 1 prospective phase II study limited to patients receiving transplants from unrelated donors [10,15-27]. The largest study to date, from the European Group for Blood and Marrow Transplantation [15], included 229 patients with a heterogeneous pretransplantation disease status. The most common limitation was the high rate of disease progression, particularly in patients with advanced disease and in heavily pretreated patients; other important open questions were the increased NRM in patients receiving transplants from unrelated donors and the high morbidity due to chronic GVHD in elderly recipients.

Salvage treatment with novel agents and RIC allo-SCT are not alternative therapies per se. It can be hypothesized that the use of a salvage treatment incorporating novel agents followed by RIC allo-SCT at the time of the first relapse after auto-SCT can provide good disease control. To evaluate RIC allo-SCT as a realistic salvage option in the clinical setting of relapsed MM, we performed a retrospective analysis in patients who relapsed after single or tandem auto-SCT and were treated with novel agents. The participating centers were 7 hematologic institutions that in the last decade have independently adopted a policy of HLA-typing patients and their siblings and/or starting an unrelated donor search soon after failure of auto-SCT because of the intention to proceed to allo-SCT. Our study was structured similarly to an intention-to-treat analysis; outcomes were compared in patients in whom a sibling or unrelated donor had been identified (donor group) and those without a suitable donor (no-donor group). The objective of the study was to examine whether having a donor might be beneficial for the outcome of patients with MM who relapsed after treatment with a salvage therapy incorporating novel agents at the time of the first relapse after auto-SCT.

PATIENTS AND METHODS

Patients

Between 2002 and 2008, in the 7 participating centers, a total of 619 patients with newly diagnosed MM underwent single or tandem auto-SCT, 291 of whom relapsed after autografting. Of these patients, 169 fullfilled the study criteria and were enrolled in this retrospective study. The study design was approved by the Institutional Review Boards of all 7 participating institutions. This study was structured as follows. First, a synopsis of the study was sent to the centers. After agreeing to join the study, a center received a letter explaining how to collect the data required on a specific patient form. Each center designated an investigator in charge of the study. Each center reviewed all of the patients with MM who relapsed after single or tandem auto-SCT between 2002 and 2008, including those patients who had a clinical relapse requiring treatment, received a single salvage treatment including new drugs (thalidomide or lenalidomide or bortezomib), and underwent HLA typing within 30 days after the relapse date with the aim of identifying a sibling and/or unrelated donor and performing an allo-SCT within 1 year after relapse. The patient forms returned by the centers were reviewed by a statistician and a senior hematologist, and, if necessary, specific queries were sent back to the centers.

Disease response was evaluated through clinical examination, blood chemistry tests, bone marrow biopsy analysis, and imaging techniques (whole-skeleton X-ray and spinal magnetic resonance imaging, according to each center's policy). In cases of clinically suspected extramedullary disease, appropriate imaging techniques (magnetic resonance imaging, computed tomography, or 18F-fluorodeoxyglucose positron emission tomography) and/or needle aspiration or biopsy were performed at the discretion of the attending physician. Karyotype at diagnosis was detected by fluorescence in situ hybridization, if available, to assess the following baseline abnormalities: t(14;14), deletion

17p13, and deletion 13q14. The presence of these abnormalities identified a high-risk karyotype. Response was evaluated according to the international uniform response criteria for MM [28].

A search for a sibling donor was performed in all 169 enrolled patients, and another search for a suitable unrelated donor was performed in 110 patients. The search for an unrelated donor was not initiated in 59 patients because of the availability of an HLA-matched sibling donor (n = 28), patient refusal (n = 6), or medical decision (n = 25). The attending physicians decided to avoid the search for an unrelated donor because of the following reasons: patient age ≥60 years at relapse (n = 18), previous solid cancer (n = 3), or poor cardiac or lung function (n = 4).

A total of 75 patients (44%) had a suitable donor, and 94 (56%) did not. The latter patients were treated according to the protocol of each center, with salvage therapy continued as long as it was clinically required (Figure 1).

Sixty-eight of the 75 patients with a donor (91%) underwent allo-SCT (Table 1). Seven of these 75 patients (9%) did not receive the planned allo-SCT and thus were excluded from the analysis of outcome restricted to the allo-SCT patients, although they were included in the donor versus no-donor analysis. Reasons for not receiving allo-SCT were disease progression (n = 4) and serious comorbidities (n = 3). Twenty-four of the patients undergoing allo-SCT (35%) had an HLA-identical sibling donor, and 44 (65%) had an unrelated donor. For unrelated donors, HLA typing for HLA-A, -B, -C, and -DRB1 loci was required. Thirty unrelated donors had a known HLA match; 24 of these donors were full 10/10 allele HLA-matched, and the other 6 had a single antigen mismatch in major histocompatibility complex class I. Fifty-seven patients (84%) received peripheral stem cells, and 11 (16%) received bone marrow. Preparative regimens before allo-SCT were either RIC or nonmyeloablative (NMA). These regimens included fludarabine and melphalan with or without thiotepa in 28 patients (41%), fludarabine plus 2 Gy

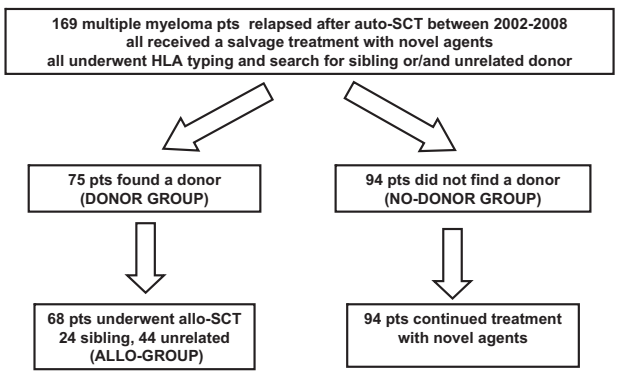

Figure 1. Flow chart of the study.

Table 1. Characteristics of the Patients Who Underwent Allo-SCT (n = 68)

Time from diagnosis to allo-SCT, months, median (range)	36 (9-168)
Donor, n (%)	
HLA-matched sibling	24 (35)
Unrelated	44 (65)
HLA matching, n (%)	
HLA-matched sibling	24 (44)
HLA-matched unrelated	24 (44)
HLA-mismatched unrelated	6 (12)
Missing	14
Source, n (%)	
Bone marrow	11 (16)
Peripheral blood	57 (84)
Conditioning regimen, n (%)	
Fludarabine, melphalan ± thiotepa	28 (41)
Fludarabine + 2 Gy TBI	24 (35)
Fludarabine + treosulfan	6 (9)
Fludarabine + cyclophosphamide	5 (7)
Busulfan-melphalan	2 (3)
Fludarabine + melphalan + 2 Gy TBI	2 (3)
Fludarabine + melphalan + 2 Gy TBI	1 (2)
ATG, n (%)	21 (31)
Acute GVHD, n (%)	
Grade 0-I	40 (59)
Grade II-IV	28 (41)
Chronic GVHD, n (%)	
Absent	32 (61)
Limited	6 (11)
Extensive	15 (28)
Not evaluable	15
DLI, n (%)	12 (18)
Antimyeloma treatment after allo-SCT, n (%)	36 (53)

total body irradiation (TBI) in 24 cases (35%), fludarabine and cyclophosphamide in 5 patients (7%), fludarabine and treosulfan in 6 patients (9%), and other combinations in 5 patients. GVHD prophylaxis consisted of cyclosporine plus methotrexate in 44 patients and mycophenolate mofetil in 24 patients, with the addition of antithymocyte globulin (ATG) in 21 of the 44 transplants from unrelated donors. Acute and chronic GVHD were graded according to standard international criteria [29,30].

Statistical Analysis

Data were collected in an XLS database and imported into Stata/SE 9.0 for Windows (StataCorp, College Station, TX) for statistical analysis. The close-out date for analysis was December 2010. Two analyses were performed: a so-called "donor versus no-donor" analysis to compare the outcomes of patients based on the availability of a donor, and an analysis limited to patients undergoing allo-SCT to assess the outcome RIC allo-SCT in patients with MM. The starting points of our analyses were the day of relapse after auto-SCT for the comparison of the donor and no-donor groups and the day of allo-SCT for the analysis restricted to the patients undergoing allo-SCT.

NRM was defined as death due to all causes not related to myeloma. The cumulative incidence method

was used to estimate the rate of acute and chronic GVHD, NRM, and relapse. Overall survival (OS) was defined as the time (in months) from the aforementioned starting points to either death or the last observation. Progression-free survival (PFS) was defined as the time from these starting points to relapse, progression, death, or last observation. In the allo-SCT group, salvage treatment consolidated by allo-SCT was considered a unique treatment; thus, relapse or progression was determined at the time of the first evaluation after allo-SCT.

OS and PFS were described using the Kaplan-Meier approach. The cumulative incidence method was used to estimate relapse and NRM, accounting for the presence of competing risks. Quantitative variables were tested for normal distribution using the Kolmogorov-Smirnov test. Comparisons between groups were performed using the *t* test or the Mann-Whitney *U* test, depending on the Kolmogorov-Smirnov test results. The χ^2 test was used to analyze categorical values; when assumptions for χ^2 tests were not verified, the Fisher exact test was used. Based on the method of Fine and Gray (1999), competing-risk regression was used to compare relapse and NRM in the donor and no-donor groups. OS and PFS were analyzed using Cox proportional hazard models, after the proportional hazards assumption had been verified.

In univariate analysis, variables considered as possible prognostic factors were age at transplantation (years), year of diagnosis (before 2000, 2000-2003, 2004 and after), interval between diagnosis and auto-SCT (months), type of monoclonal gammopathy (IgG, IgA, Bence-Jones, or nonsecretory), Durie and Salmon stage (I, II, or III), karyotype at diagnosis (high risk or standard risk), number of auto-SCTs (single or double procedure), induction before auto-SCT (conventional agent or novel drugs), extramedullary myeloma at relapse (present or absent), interval between auto-SCT and relapse (months), interval between relapse and start of salvage treatment (months), type of salvage treatment (thalidomide-based, bortezomib-based, or lenalidomide-based), duration of salvage treatment (months), and response to salvage treatment (responsive or unresponsive). In the patients undergoing allo-SCT, time between diagnosis and allo-SCT (months), disease status before SCT (responsive or unresponsive), type of conditioning regimen (RIC versus NMA), donor (sibling or unrelated), HLA typing (HLA-matched related versus HLA-matched unrelated versus HLA-mismatched unrelated), stem cell source (bone marrow or peripheral blood), ATG (yes or no), acute GVHD (grade 0-I or grade II-IV), chronic GVHD (absent or present), and donor lymphocyte infusion (DLI; yes or no) were considered as possible prognostic factors.

Acute and chronic GVHD were treated as time-dependent variables. Multivariate stepwise analyses included all variables found to be significant at $P \leq .10$ on univariate analysis. Retention in the stepwise model required that the variable be significant at $P \leq .05$ in multivariate analysis.

RESULTS

Donor versus No-Donor Analysis: Comparison of Patient Clinical Characteristics at Diagnosis and at Relapse

The median patient age was significantly younger in the donor group compared with the no-donor group (55 versus 59 years; $P \leq .001$); however, the 2 groups had similar main clinical characteristics at diagnosis and at relapse (Tables 2 and 3). In fact, no significant differences were detected between the 2 groups with regard to type of M-component, MM stage at diagnosis, high-risk karyotype at diagnosis, or year of MM diagnosis, but the prevalence of extramedullary manifestations was significantly higher in the donor group (21% versus 9%; $P = .042$). The median time between auto-SCT and relapse was 16 months in the donor group and 17.5 months in the no-donor group ($P = .363$), and the median interval between relapse and the start of salvage treatment was ≤1 month in both groups ($P = .124$). The type of salvage therapy administered was not significantly different in the 2 groups, with thalidomide-based regimens in 52% of the donor group and 39% of the no-donor group,

Table 2. Clinical Characteristics of the Patients at Diagnosis and at the Time of Auto-SCT

	Donor Group	No-Donor Group	*P*
Number of patients	75	94	
Age at auto-SCT, years, median (range)	55 (34-68)	59 (31-73)	<.001
M-component, n (%)			
IgG	41 (55)	46 (50)	.164
IgA	8 (11)	22 (23)	
Bence-Jones protein	17 (22)	19 (20)	
Other or nonsecretory	9 (12)	7 (7)	
Stage, n (%)			
I	6 (8)	5 (6)	
II	8 (11)	18 (19)	.274
III	61 (81)	71 (75)	
Karyotype, n (%)			
Standard risk	20 (60)	20 (57)	.772
High risk	13 (40)	15 (43)	
Missing	42	59	
Diagnosis year, n (%)			
≤2000	21 (28)	16 (17)	.188
2001-2003	21 (28)	40 (43)	
≥2004	33 (44)	38 (40)	
Time from diagnosis to auto-SCT, months, median (range)	8 (3-115)	8 (2-119)	.274
Induction before auto-SCT, n (%)			
Conventional agents	34 (72)	77 (82)	.190
Novel agents	13 (28)	17 (18)	
Missing	28	0	
Tandem auto-SCT, n (%)	45 (60)	65 (69)	.215

Table 3. Clinical Characteristics of the Patients at Relapse

	Donor Group	No-Donor Group	*P*
Number of patients	75	94	
Time from auto-SCT to relapse, months, median (range)	16 (2-87)	17.5 (2-88)	.363
Time from relapse to treatment, months, median (range)	1 (0-23)	1 (0-51)	.124
Clinical features at relapse, n (%)			
Presence of extramedullary MM	10 (21)	8 (9)	.042
Absence of extramedullary MM	37 (79)	82 (91)	
Missing	28	4	
Treatment of relapse, n (%)			
Thalidomide-based	39 (52)	37 (39)	
Bortezomib-based	25 (33)	31 (33)	
Lenalidomide-based	7 (9)	17 (18)	.194
Other drugs	4 (6)	9 (10)	
Treatment duration, months, median (range)	4 (1-52)	5 (1-55)	.497
Response to relapse treatment, n (%)			
Missing	15	9	
CR + VGPR	20 (33)	25 (29)	.09
PR	28 (47)	27 (32)	
Resistance	7 (12)	16 (19)	
Progression	5 (8)	17 (20)	

bortezomib-based regimens in 33% of the donor group and 33% of the no-donor group, lenalidomide-based regimens in 9% of the donor group and 18% of the no-donor group, and other therapies in 6% of the donor group and 10% of the no-donor group. The median duration of salvage treatment was 4 months in the donor group and 5 months in the no-donor group ($P = .497$). The quality of response after salvage treatment did not differ significantly between the 2 groups (complete response [CR] + very good partial response [VGPR], 33% versus 29%; partial response [PR], 47% versus 32%; resistance, 12% versus 19%; progression, 8% versus 20%; $P = .09$).

Survival Curves

The median follow-up after the beginning of salvage treatment was 19 months (range, 1-97 months) in all patients and 29 months (range, 6-88 months) in surviving patients. At the last follow-up, 27 of 75 patients (36%) in the donor group and 24 of 94 patients (26%) in the no-donor group were alive and maintained a clinical response (CR + PR). Overall, 111 of 169 patients (66%) progressed or relapsed after therapy. For all patients, the median PFS was 12 months (range, 1-88 months), and the median OS was 19 months (range, 1-97 months). The 2-year cumulative incidence of relapse was 41% in the donor group and 81% in the no-donor group (sub-hazard ratio, 3.148; 95% confidence interval [CI], 2.098-4.721; $P < .0001$) (Figure 2A) The 2-year PFS was 42% in the donor group and 18% in the no-donor group (hazard ratio [HR], 2.018; 95% CI, 1.392-2.926; $P < .0001$) (Figure 2B). The 2-year OS was 54% in the donor group and 53% in the no-donor group (HR, 1.233; 95% CI, 0.809-1.879; $P = .329$) (Figure 2C).

Novel agents associated with steroids or other drugs were administered as second-line salvage treatment in 23 of 25 patients (91%) of the donor group and 44 of 52 patients (84%) of the no-donor group and as third-line salvage treatment in 6 of 9 patients (67%) of the donor group and 17 of 33 patients (51%) of the no-donor group.

Prognostic factors that were significantly ($P \leq .10$) associated with PFS in the univariate proportional hazards model were unavailability of a donor (HR, 2.02; 95% CI, 1.39-2.92; $P < .001$), duration of salvage treatment (HR, 0.96; 95% CI, 0.94-0.99; $P = .005$),

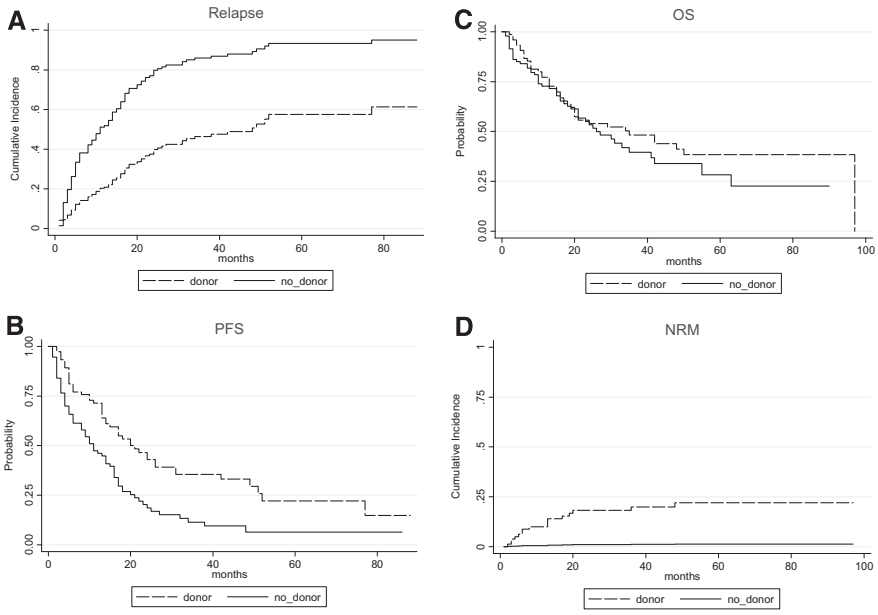

Figure 2. Comparisons between donor and no-donor groups. (A) Incidence of relapse ($P < .0001$). (B) PFS ($P < .0001$). (C) OS ($P = .329$). (D) NRM ($P = .0004$).

and unresponsiveness to salvage treatment (HR, 2.27; 95% CI, 1.81-4.09; $P < .001$). The variables that showed a significant association with OS in the univariate analysis were abnormal karyotype at diagnosis (HR, 2.42; 95% CI, 1.17-4.99; $P = .017$), double auto-SCT (HR, 1.49; 95% CI, 0.96-2.35; $P = .079$), duration of salvage treatment (HR, 0.95; 95% CI, 0.91-0.98; $P = .004$), and unresponsiveness to salvage treatment (HR, 3.68; 95% CI, 2.29-5.90; $P < .001$). Other clinical features of MM, such as patient age, year of diagnosis, interval between diagnosis and auto-SCT, type of monoclonal gammopathy, stage, type of induction therapy, extramedullary relapse, and interval between auto-SCT and relapse, were not significant predictors for PFS and OS in univariate analysis. In multivariate analysis, donor unavailability was a significant unfavorable factor for PFS (HR, 2.86; 95% CI, 1.84-4.43), but not for OS (Table 4). Lack of chemosensitivity after salvage treatment significantly reduced both PFS and OS (HR, 2.37; 95% CI, 1.57-3.58 and HR, 3.81; 95% CI, 1.76-8.24, respectively). Moreover, high-risk karyotype at diagnosis and previous treatment with double auto-SCT versus single auto-SCT had a significant negative impact on OS (HR, 2.37; 95% CI, 1.13-4.96 and HR 2.83; 95% CI, 1.04-7.69, respectively). The only protective factor identified was a longer duration of salvage treatment, which was associated with better PFS (HR, 0.96; 95% CI, 0.93-0.98).

Toxicity and NRM

A total of 91 of 169 patients (54%) died after treatment. The causes of death were progressive disease in 73 patients (43%) and toxicity in 18 patients (11%). Forty-one of 75 patients (55%) in the donor group died, 24 from myeloma (32%) and 17 from toxicity (23%). In the no-donor group, 50 of 94 patients (53%) died, 49 (52%) due to disease and 1 (1%) due to toxicity. The 2-year cumulative incidence of NRM was 22% in the donor group and 1% in the no-donor group (sub-hazard ratio, 0.049; 95% CI, 0.006-0.381; $P = .0004$) (Figure 2D).

Outcome of Patients Undergoing Allo-SCT

A total of 68 of 75 patients (91%) with a donor proceeded to RIC allo-SCT. The median time between HLA typing and allo-SCT was 8 months (range, 3-30 months); 52 of 68 patients (76%) underwent transplantation within 12 months, and 16 of 68 (24%) did so within 24 months. At the last follow-up, 19 of 68 patients (28%) were alive in stringent CR (n = 7), CR (n = 8), or VGPR (n = 4), and another 8 patients (12%) were in PR; thus, 27 patients (40%) maintained a clinical objective response. The median observed PFS was 13 months, with an estimated 1-year PFS of 64% and 2-year PFS of 38%. The median observed OS was 35 months, with an estimated 1-year OS of 73% and 2-year OS of 55% (Figure 3). Thirty-six patients (48%) died, 19 (25%) due to disease progression and 17 (23%) due to transplantation-related causes. This translates to a 1-year NRM of 18% and 2-year NRM of 22%. Grade II-IV acute GVHD was seen in 28 evaluable patients (41%), and chronic GVHD was seen in 21 (39%).

Thirty patients (44%) experienced relapse or progression after allo-SCT. Twelve patients received a median of 1 DLI (range, 1-15) in association with 1 or more new drugs (thalidomide in 4 patients; bortezomib in 8 patients; lenalidomide in 1 patient) because of persistent MM (3 patients) or relapse (9 patients). Four of these 12 patients (30%) had a long-term response and were alive at a median follow-up of 30 months (range, 13-46 months). Another 24 patients received an antimyeloma drug after allo-SCT for maintenance (3 patients) or treatment of relapse (21 patients).

Prognostic factors that were significantly ($P \leq .10$) associated with PFS in the univariate proportional hazards model were interval between diagnosis and

Table 4. Multivariate Analysis of PFS and OS Data

	PFS			OS		
Factor	HR	95% CI	P	HR	95% CI	P
Donor						
Donor	1					
No donor	2.860	1.844-4.435	<.001			
Abnormal karyotype						
Standard risk				1		
High-risk				2.368	1.130-4.965	.022
Auto-SCT						
Single				1		
Double				2.835	1.045-7.690	.041
Duration of salvage treatment, months*	0.956	0.931-0.982	.001			
Response to salvage treatment						
Responsive	1			1		
Nonresponsive or progressive	2.373	1.574-3.577	<.001	3.809	1.762-8.236	<.001

*Modeled as a continuous variable.

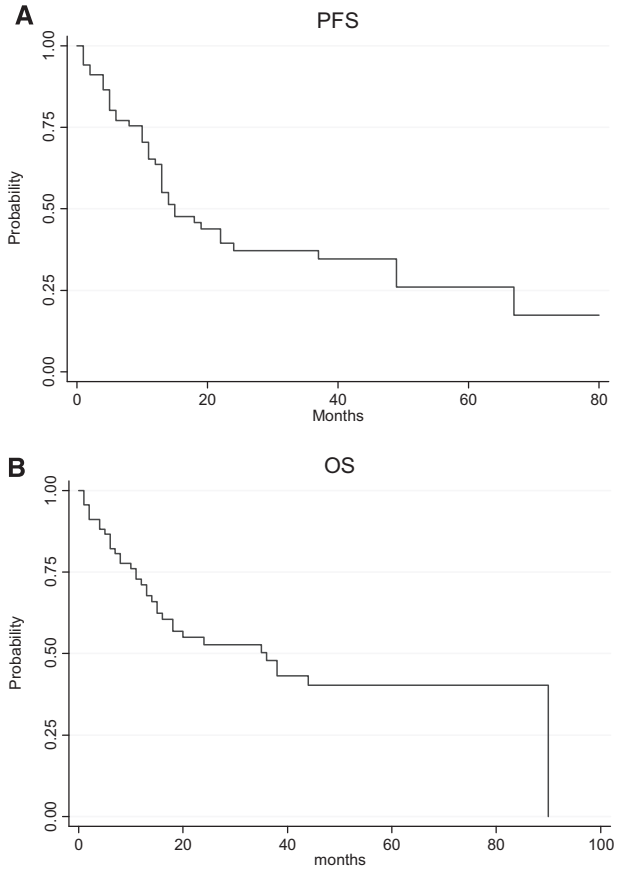

Figure 3. PFS (A) and OS (B) curves of patients who underwent allo-SCT.

allo-SCT (HR, 1.01; 95% CI, 1.00-1.02; $P = .08$), progressive disease before transplantation (HR, 4.27; 95% CI, 1.01-16.56; $P = .04$), and development of chronic GVHD (HR, 0.43; 95% CI, 0.18-1.04; $P = .06$). The final survival model showed no significant prognostic factors for PFS. The variables with a significant association with OS in the univariate analysis were interval between auto-SCT and relapse (HR, 1.012; 95% CI, 1.00-1.04; $P = .08$), progressive disease before transplantation (HR, 3.74; 95% CI, 0.81-17.28; $P = .09$), T cell depletion with ATG (HR, 0.52; 95% CI, 0.26-1.05; $P = .07$), and development of chronic GVHD (HR, 0.32; 95% CI, 0.10-0.95; $P = .04$). In multivariate analysis, development of chronic GVHD maintained a protective effect on OS (HR, 0.11; 95% CI, 0.17-0.68; $P = .02$), whereas an increased interval between auto-SCT and relapse was associated with poor OS (HR, 1.07; 95% CI, 1.01-1.13; $P = .02$). In univariate analysis, no significant predictors for NRM were identified among the main clinical features of patients and transplants.

DISCUSSION

In the last decade, RIC regimens have allowed the use of allo-SCT in a greater number of patients with MM, even elderly and heavily pretreated patients, by reducing NRM compared with myeloablative SCT [10,15,16]. RIC allo-SCT has ensured sustained allogeneic engraftment in the majority of patients and has demonstrated the possibility of inducing an antitumor effect, even in patients with advanced disease [16]. However, as the clinical results of salvage treatment with new drugs such as bortezomib and immunomodulatory agents have become available [1-4], the initial enthusiasm over RIC allo-SCT has been replaced by some skepticism. For example, data from the registry of the Gruppo Italiano Trapianto Midollo Osseo indicates a 33% drop in the number of RIC allo-SCTs performed between 2004 and 2009. Several randomized trials of auto-SCT with or without NMA allo-SCT from HLA-identical sibling donors in newly diagnosed patients have been conducted [11-14], and superior event-free survival and OS in the allo-SCT arm have been suggested in 2 of these studies [12,13]. The incorporation of novel agents in the induction before and after auto-SCT led to further improvement in clinical results [31,32]; thus, this is considered the standard approach for patients with newly diagnosed MM, leaving upfront allo-SCT as a possible choice for selected high-risk patients enrolled in prospective clinical trials.

In patients with advanced relapse, no comparative studies of RIC allo-SCT and salvage treatment at conventional doses have been published, and retrospective data are lacking. To our knowledge, the present study is the first multicenter study comparing 2 different treatment strategies for relapsed patients: allo-RIC versus salvage treatment with new drugs. We retrospectively analyzed the data from 7 centers that between 2002 and 2008 adopted the same treatment policy of offering RIC allo-SCT to all relapsed patients age <65 years old with an available sibling or HLA-matched unrelated donor. To eliminate the possible bias due to progressive disease during the waiting time for donor identification and/or transplant procurement, a donor versus no-donor analysis of outcome was performed. The only previous study with a similar design was that of de Lavallade et al. [33]; however, their results were based on a single-center analysis of only 32 patients.

In our study, the 2 groups had similar demographic and clinical characteristics at diagnosis and at relapse. The only significant difference was the younger median age of the donor group, suggesting that younger patients have a greater likelihood of finding a suitable sibling donor and/or undergoing a search for an unrelated donor. The interval between auto-SCT and relapse was quite short in both groups (donor, 16 months; no-donor, 17.5 months) compared with the PFS reported in most trials using auto-SCT preceded by conventional chemotherapy [34,35]. In addition, the median time from detection of relapse

by blood chemistry analysis and overt clinical relapse necessitating treatment was only 1 month in both groups. These observations could suggest a possible selection of patients with high-risk relapse, for whom the attending physician was more likely to decide to search for a donor.

Our donor versus no-donor analysis showed that the 2-year relapse rate was halved and the 2-year PFS rate was significantly increased (by 20%) in the donor group compared with the no-donor group. Moreover, the lack of an HLA-matched suitable donor was a significant unfavorable prognostic factor for PFS in multivariate analysis. Unresponsiveness to salvage treatment was the other factor that significantly shortened PFS.

In the multivariate analysis on OS data, we found that having a donor had no significant impact on OS, whereas high-risk cytogenetics and unresponsiveness to salvage treatment were the main predictors of OS for the entire population. With a longer follow-up, the graft-versus-myeloma effect also might lead to a better OS for the donor group, as was demonstrated for PFS.

The statistical evidence of a poorer OS in patients who relapsed after tandem auto-SCT compared with those with single auto-SCT needs to be interpreted with caution, given that cycles of high-dose therapy were administered according to local protocols and not on the basis of an uniform strategy. In addition, the present study started only at the moment of relapse after auto-SCT.

Although the fluorescence in situ hybridization analysis was available for only 40% of the patients in this study, detection of 13q deletion, 17p deletion, or translocation (4;14) at diagnosis negatively influenced OS irrespective of treatment. It is well known that patients with high-risk karyotypes relapse earlier after single or tandem auto-SCT [36]. Some reported data suggest that treatment with bortezomib and immunomodulatory agents can overcome the negative prognostic influence of a high-risk karyotype [37-40], but these data need to be confirmed in prospective trials on larger samples stratified on the basis of specific cytogenetic abnormalities. The strong correlation between high-risk karyotype and unfavorable outcome in our study could be explained in part by the fact that the most common new drug incorporated in salvage therapies was thalidomide (52% in the donor group, 39% in the no-donor group), which has shown less-convincing efficacy data in high-risk karyotype MM compared with lenalidomide and bortezomib [40].

It is noteworthy that the quality of response after salvage treatment at the time of first relapse was the most important factor influencing OS (HR, 3.809). Although not unexpected, this finding suggests that the treatment of first relapse is critical to the subsequent outcome. Therefore, no medical and economical efforts should be spared at this time, leaving disease palliation to subsequent lines of treatment.

A minority of patients in our series had extramedullary relapses, which were more frequent in the donor group. However, extramedullary recurrences after auto-SCT neither adversely affected the outcome of the entire study population nor significantly worsened the outcome of the donor group, suggesting the efficacy of the novel agents used as salvage treatment, as reported previously [41,42], and the possible positive immunomodulating effect of allo-SCT [43].

The clinical results of allo-SCT in the present study are comparable with previously published data. We observed a 22% 1-year NRM, which is within the 15%-37% range reported in previous studies [15-26]. The NRM rate continued to increase in the second year after transplantation, probably due to chronic GVHD and infectious complications. The NRM rate was similar in sibling and unrelated transplants, as reported previously [24]; however, our data did not confirm the increased NRM risk in transplants from HLA-mismatched unrelated donors as reported by Kröger et al. [24], although there were a few such cases in our population. Nineteen of 68 patients (28%) were in continuous complete clinical remission at a median follow-up of 29 months, indicating that allo-SCT at salvage can achieve long-term disease control, confirming previously reported observations [10,20,25,26].

We found no clear advantage or disadvantage of using different conditioning regimens, including true NMA regimens (eg, fludarabine plus 2-Gy TBI) and RIC regimens with different types of alkylating agents. T cell depletion with ATG, used in approximately one-half of unrelated donor transplantations, showed a protective effect on OS in univariate analysis, suggesting a possible beneficial role, as reported by Kröger et al. [23,24]. In fact, T cell depletion with ATG did not lead to an increase in relapse rate after allo-SCT, unlike alentuzumab [15], and allowed the use of transplants from matched unrelated donors with an NRM rate comparable to that seen with sibling donors [23,24].

In this study, the immunomodulating effects of allo-SCT was demonstrated by the observation that chronic GVHD was a significant predictor for prolonged PFS and OS, in agreement with previous reports [15,17,18,20,21]. In contrast, the use of allo-SCT late in the course of disease and progressive MM before allo-SCT were unfavorable prognostic factors. A few studies suggested that a clinical response after allo-SCT could be achieved in chemorefractory myelomas as well [16], although chemosensitivity before allo-SCT emerged as a significant factor for a long-term favorable outcome in most analyses [15,17,18,21]. Moreover, the administration of DLI in association

with new drugs resulted in a durable clinical effect in 30% of patients, which is within the 30%-60% range reported in previous studies [16,18,27].

We acknowledge that our study has some limitations. First, the availability of a donor was 44% in the entire population and 54% in the group of patients who underwent a search for both sibling and unrelated donors, because 31 patients never looked for an unrelated donor due to either refusal or medical decision. This 54% donor availability is slightly inferior to the 66% reported in a retrospective study of patients with Hodgkin's lymphoma with a similar donor versus no-donor analysis [44]. However, our patients with MM were much older than the patients in that study (median age, 57 years versus 31 years) and were more likely to have old or unfit sibling donors ineligible for donation and thus never submitted to HLA typing. Second, our patients were recruited over quite a long period (between 2002 and 2008), during which diagnostic and treatment strategies changed. For example, salvage treatment with thalidomide was more frequent in the past, whereas nowadays bortezomib or lenalidomide are used more often. However, although this was a retrospective study, selection bias was minimized by the sharing of similar treatment policy and study protocol by all participating institutions. Thus, we believe that our original study design comparing outcomes in patients with donors and patients treated with the best available nontransplantation therapy can help answer a relevant question: What is the role of RIC transplantation in the management of young patients with relapsed MM?

We confirmed that the NRM of RIC allo-SCT from related and unrelated donors was lower than previously reported rates. Moreover, we observed that the association of a salvage treatment containing novel agents consolidated by RIC allo-SCT resulted in a significant prolongation of PFS in the donor group compared with the no-donor group, but the OS advantage was not significant. A longer follow-up likely is needed to demonstrate a significant survival advantage for the donor group. The protective effect of chronic GVHD in patients undergoing allo-SCT and the clinical response to DLI suggest a possible graft-versus-myeloma effect, even in the relapse setting.

Our results indicate that allo-SCT can be an option in young patients with relapsed MM and a suitable donor. However, as recently recommended by the International Working Group Consensus statement [45], new strategies should be explored in prospective trials in selected groups of patients with the aim of reducing NRM and relapse rates. Selection of patients with chemosensitive disease, earlier planning of allo-SCT, and incorporation of DLI and novel agents as consolidation/maintenance after allo-SCT are some suggested lines of investigation in prospective studies to improve clinical results.

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